Complete Summary

GUIDELINE TITLE

Allergen immunotherapy: a practice parameter second update.

BIBLIOGRAPHIC SOURCE(S)

Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. Allergen immunotherapy: a practice parameter second update. J Allergy Clin Immunol 2007 Sep;120(3 Suppl):S25-85. [352 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Allergen immunotherapy: a practice parameter. American Academy of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 2003 Jan;90(1 Suppl 1):1-40. [210 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Immunoglobulin E (IgE)-mediated conditions:

- Allergic rhinitis (including allergic conjunctivitis)
- Allergic asthma
- Stinging insect (e.g., Hymenoptera) sensitivity

GUIDELINE CATEGORY

Counseling
Diagnosis
Evaluation
Management
Prevention
Risk Assessment
Treatment

CLINICAL SPECIALTY

Allergy and Immunology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity
- To establish guidelines for the safe and effective use of allergen immunotherapy, while reducing unnecessary variation in immunotherapy practice

TARGET POPULATION

Patients with allergic rhinitis/conjunctivitis, allergic asthma, or stinging insect (Hymenoptera) sensitivity who have demonstrable evidence of specific immunoglobulin E antibodies to relevant allergens

INTERVENTIONS AND PRACTICES CONSIDERED

1. Evaluation of patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma or stinging insect allergy
2. Immediate hypersensitivity skin testing or *in vitro* testing for specific immunoglobulin E antibodies
3. Assessment of risks, benefits and costs of appropriate management options
4. Obtaining informed consent
5. Counseling and educating patients about benefits and risk of immunotherapy
6. Allergen selection and handling
7. Establishing starting dose and immunotherapy schedule
8. Administering immunotherapy with appropriate safety equipment and procedures in place
9. Management of reactions to immunotherapy injections
10. Use of premedication
11. Follow-up for clinical response and continuation of immunotherapy treatment
12. Special considerations for immunotherapy in children, the elderly, and the pregnant patient and in patients with immunodeficiency and autoimmune disorders

Note: The following were considered, but not recommended:

- Immunotherapy for food allergy, urticaria, and atopic dermatitis
- Repetitive skin testing for measuring efficacy
- Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual)

MAJOR OUTCOMES CONSIDERED

- Efficacy of immunotherapy
    - Symptom improvement as measured by self-report of symptom scores
    - Reduction in medication as measured by medication scores and pulmonary function tests
    - Organ challenge and immunologic changes in cell markers and cytokine profiles
    - Quality of life
    - Clinical remission
- Safety of immunotherapy (e.g., rates of adverse events)

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus
Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Category of Evidence

Ia Evidence from meta-analysis of randomized controlled trials

Ib nbsp; Evidence from at least 1 randomized controlled trial

IIa Evidence from at least 1 controlled study without randomization

IIb Evidence from at least 1 other type of quasi-experimental study

III Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies

IV Evidence from expert committee reports or opinions, clinical experience of respected authorities, or both

LB Evidence from laboratory-based studies

NR Not rated

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Published clinical studies were rated by category of evidence and used to establish the strength of a clinical recommendation. Laboratory-based studies were not rated.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This document was developed by the Joint Task Force on Practice Parameters, which represents the American Academy of Allergy, Asthma and Immunology (AAAAI); the American College of Allergy, Asthma and Immunology (ACAAI); and the Joint Council of Allergy, Asthma and Immunology (JCAAI). This document builds on the previous Joint Task Force document, "Allergen immunotherapy: a practice parameter" published in the Annals of Allergy, Asthma and Immunology in 2003. The updated practice parameters draft was prepared, and the Joint Task Force reworked the initial draft into a working draft of the document.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of Recommendations

A Directly based on category I evidence

B Directly based on category II evidence or extrapolated from category I evidence

C Directly based on category III evidence or extrapolated from category I or II evidence

D Directly based on category IV evidence or extrapolated from category I, II, or III evidence

NR Not rated

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

These guidelines have undergone an extensive peer-review process consistent with recommendations of the American College of Medical Quality's "Policy on development and use of practice parameters for medical quality decision-making" (see Appendix 1 in the original guideline document).

The working draft of "Allergen immunotherapy: a practice parameter second update" was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the American College of Allergy, Asthma and Immunology (ACAAI), American Academy of Allergy, Asthma and Immunology (AAAAI), and the Joint Council of Allergy, Asthma and Immunology (JCAAI). In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. The authors carefully considered all of these comments in preparing the final version.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Guideline recommendations are presented in the form of summary statements. After each statement is a letter in parentheses that indicates the strength of the recommendation. Grades of recommendations (A-D) and categories of evidence (Ia, Ib, IIa, IIb, III, IV, LB [evidence from laboratory-based studies], and NR [Not rated]) are defined at the end of the "Major Recommendations" field.

An algorithm is also provided in the original guideline document for the appropriate use of allergen immunotherapy. Given below are annotations for use with that algorithm.

Annotations

1. Immunotherapy is effective in the management of allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity. Allergen

immunotherapy might prevent the development of asthma in individuals with allergic rhinitis. Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific immunoglobulin E [IgE] antibody).

2. Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although in vitro testing for specific IgE antibodies is useful under certain circumstances. Immunotherapy should be considered when positive test results for specific IgE antibodies correlate with suspected triggers and patient exposure.
3. Immunotherapy should not be given to patients with negative test results for specific IgE antibodies or those with positive test results for specific IgE antibodies that do not correlate with suspected triggers, clinical symptoms, or exposure. This means that the presence of specific IgE antibodies alone does not necessarily indicate clinical sensitivity. There is no evidence from well-designed studies that immunotherapy for any allergen is effective in the absence of specific IgE antibodies.
4. Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management options. Each of the 3 major management approaches (allergen immunotherapy, allergen exposure reduction, and pharmacotherapy) has benefits, risks, and costs. Furthermore, the management plan must be individualized, with careful consideration given to patient preference. Disease severity and response (or lack of response) to previous treatment are important factors.
5. The physician and patient should discuss the benefits, risks, and costs of the appropriate management options and agree on a management plan. On the basis of clinical considerations and patient preference, allergen immunotherapy might or might not be recommended. Patients with allergic rhinitis/conjunctivitis or allergic asthma whose symptoms are not well controlled by medications or avoidance measures or require high medication doses, multiple medications, or both to maintain control of their allergic disease might be good candidates for immunotherapy. Patients who experience adverse effects of medications or who wish to avoid or reduce the long-term use of medications are good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).
6. After careful consideration of appropriate management options, the physician and patient might decide not to proceed with immunotherapy.
7. Before immunotherapy is started, patients should understand its benefits, risks, and costs. Counseling should also include the expected onset of efficacy and duration of treatment, as well as the risk of anaphylaxis and importance of adhering to the immunotherapy schedule.
8. The physician prescribing immunotherapy should be trained and experienced in prescribing and administering immunotherapy. The prescribing physician must select the appropriate allergen extracts on the basis of that particular patient's clinical history and allergen exposure history and the results of tests for specific IgE antibodies. The quality of the allergen extracts available is an important consideration. When preparing mixtures of allergen extracts, the

prescribing physician must take into account the cross-reactivity of allergen extracts and the potential for allergen degradation caused by proteolytic enzymes. The prescribing physician must specify the starting immunotherapy dose, the target maintenance dose, and the immunotherapy schedule (see the "Immunotherapy Schedules and Doses" section below under Summary Statements and in the original guideline document). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; e.g., for dust mite) or bioequivalent allergy units (BAU; e.g., for grass) for standardized allergen extracts. For nonstandardized extracts, a suggested maintenance dose is 3000 to 5000 protein nitrogen units (PNU) or 0.5 mL of a 1:100 weight/volume (wt/vol) dilution of manufacturer's extract. If the major allergen concentration of the extract is known, a range between 5 and 20 micrograms of major allergen is the recommended maintenance dose for inhalant allergens and 100 micrograms for Hymenoptera venom. Immunotherapy treatment can be divided into 2 periods, which are commonly referred to as the *build-up* and *maintenance phases*.

The immunotherapy build-up schedule (also referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 to 28 weeks. In conventional schedules a single dose increase is given on each visit, and the visit frequency can vary from 1 to 3 times a week. Accelerated schedules, such as rush or cluster immunotherapy, entail administration of several injections at increasing doses on a single visit. Accelerated schedules offer the advantage of achieving the therapeutic dose earlier but might be associated with increased risk of systemic reaction in some patients.

9. Immunotherapy should be administered in a setting that permits the prompt recognition and management of adverse reactions. The preferred location for such administration is the prescribing physician's office. However, patients can receive immunotherapy injections at another health care facility if the physician and staff at that location are trained and equipped to recognize and manage immunotherapy reactions, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

   In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring peak expiratory flow rate before administering an immunotherapy injection and withholding an immunotherapy injection if the peak expiratory flow rate is considered low for that patient. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

10. Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.
11. Local reactions can be managed with local treatment (e.g., cool compresses or topical corticosteroids) or antihistamines. Systemic reactions can be mild

or severe (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly, although subcutaneous administration is acceptable.

Antihistamines and systemic corticosteroids are secondary medications that might help to modify systemic reactions but should never replace epinephrine in the treatment of anaphylaxis. Intravenous saline or supplemental oxygen might be required in severe cases. For additional details, see the practice parameters for anaphylaxis.

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

12. Patients receiving maintenance immunotherapy should have follow-up visits at least every 6 to 12 months. Periodic visits should include a reassessment of symptoms and medication use, the medical history since the previous visit, and an evaluation of the clinical response to immunotherapy. The immunotherapy schedule and doses, reaction history, and patient compliance should also be evaluated. The physician can at this time make adjustments to the immunotherapy schedule or dose, as clinically indicated.

    There are no specific markers that will predict who will remain in clinical remission after discontinuing effective allergen immunotherapy. Some patients might sustain lasting remission of their allergic symptoms after discontinuing allergen immunotherapy, but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy. As with the decision to initiate allergen immunotherapy, the decision to discontinue treatment should be individualized, taking into account factors such as the severity of the patient's illness before treatment, the treatment benefit sustained, and the inconvenience immunotherapy represents to a specific patient and the potential effect a clinical relapse might have on the patient. Ultimately, the duration of immunotherapy should be individualized on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

Summary Statements

Mechanisms of Immunotherapy

1. Immunologic changes during immunotherapy are complex. (**D**)
2. Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. (**A**)
3. Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+$ $CD25^+$ regulatory T lymphocytes. (**A**)

4. Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. (**A**)
5. Increases in allergen-specific immunoglobulin G (IgG) antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. (**A**)

Allergen Extracts

6. When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. (**A**)
7. Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. (**B**)
8. In choosing the components for a clinically relevant allergen immunotherapy extract, the physician should be familiar with local and regional aerobiology and indoor and outdoor allergens, paying special attention to potential allergens in the patient's own environment. (**D**)

Cross-Reactivity of Allergen Extract

9. Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. (**B**)

Efficacy of Immunotherapy

Allergic Rhinitis, Allergic Asthma, and Stinging Insect Hypersensitivity

10. Immunotherapy is effective for treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, and stinging insect hypersensitivity. Therefore immunotherapy merits consideration in patients with these disorders as a possible treatment option. (**A**)

Food Allergy, Urticaria, and Atopic Dermatitis

11. Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. (**D**)

    There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. (**C**)

    The potential for benefit in symptoms related to oral allergy syndrome with inhalant immunotherapy directed at the cross-reacting pollens has been observed in some studies but not in others. For this reason, more investigation is required to substantiate that a benefit in oral allergy symptoms will occur with allergen immunotherapy. (**C**)

Measures of Efficacy

12. Clinical parameters, such as symptoms and medication use, might be useful measures of the efficacy of immunotherapy in a clinical setting; however, repetitive skin testing of patients receiving immunotherapy is not recommended. (**A)**

Safety of Immunotherapy

Reaction Rates

13. Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. (**C**)
14. Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. (**C**)
15. An assessment of the patient's current health status should be made before administration of the allergy immunotherapy injection to determine whether there were any recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (e.g., peak flow) for the asthmatic patient before allergy injections. (**B**)

Timing of Anaphylactic Reactions to Immunotherapy Injections

16. Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. (**C**)

Beta-Adrenergic Blocking Agents

17. Beta-adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of beta-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require beta-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. (**C**)

Contraindications

18. Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications for

allergen immunotherapy. Examples include severe asthma uncontrolled by pharmacotherapy and significant cardiovascular disease. (**C**)

Reducing the Risk of Anaphylaxis to Immunotherapy Injections

19. Allergen immunotherapy should be administered in a setting where procedures that can reduce the risk of anaphylaxis are in place and where the prompt recognition and treatment of anaphylaxis is ensured. (**C**)

Patient Selection

Clinical Indications

20. Allergen immunotherapy should be considered for patients who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. (**A**)

Special Precautions in Patients with Asthma

21. Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. (**C**)

Clinical Indications for VIT (Venom Immunotherapy)

22. VIT should be strongly considered if the patient has had a systemic reaction to a Hymenoptera sting, especially if such a reaction was associated with respiratory symptoms, cardiovascular symptoms, or both and if the patient has demonstrable evidence of specific IgE antibodies. (**A**)
23. Patients selected for immunotherapy should be cooperative and compliant. (**D**)

Allergen Selection and Handling

Clinical Evaluation

24. The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. (**A**)

Clinical Correlation

25. The allergen immunotherapy extract should contain only clinically relevant allergens. (**A**)

Skin Tests and in vitro IgE Antibody Tests

26. Skin testing has been the primary diagnostic tool in clinical studies of allergen immunotherapy. Therefore in most patients, skin testing should be used to determine whether the patient has specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. (**A**)

Specific Allergens

27. Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, and Hymenoptera hypersensitivity. Therefore immunotherapy should be considered as part of the management program in patients who have symptoms related to exposure to these allergens, supported by the presence of specific IgE antibodies. (**A**)

Principles of Mixing

28. Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. (**B**)

Mixing Cross-Reactive Extracts

29. The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. Many botanically related pollens contain allergens that are cross-reactive. When pollens are substantially cross-reactive, selection of a single pollen within the cross-reactive genus or subfamily might suffice. When pollen allergens are not substantially cross-reactive, testing for and treatment with multiple locally prevalent pollens might be necessary. (**B**)

Dose Selection

30. The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. (**A**)

Proteolytic Enzymes and Mixing

31. Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. (**B**)
32. Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. (**D**)

Allergen Immunotherapy Extract Handling

<u>Storage</u>

33. Allergen immunotherapy extracts should be stored at 4 degrees Celsius (C) to reduce the rate of potency loss. (**B**)

    Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions. It is the responsibility of

each supplier or manufacturer to ship extracts under validated conditions that are shown not to adversely affect the product's potency or safety. (**C**)

Storing Dilute Extracts

34. More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. (**B**)

    In determining the allergen immunotherapy extract expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of factors separately and collectively, including (1) storage temperature, (2) presence of stabilizers and bactericidal agents, (3) concentration, (4) presence of proteolytic enzymes, and (5) volume of the storage vial. (**B**)

Immunotherapy Schedules and Doses

35. A customized individual allergen immunotherapy extract should be prepared from a manufacturer's extract or extracts in accordance to the patient's clinical history and allergy test results and might be based on single or multiple allergens. (**D**)

Maintenance Concentrate

36. The highest-concentration allergy immunotherapy vial (e.g., 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. The maintenance dose is the dose that provides therapeutic efficacy without significant adverse local or systemic reactions and might not always reach the initially calculated projected effective dose. This reinforces that allergy immunotherapy must be individualized. (**D**)

Recommended Doses

37. The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. (**A**)

Effect of Dilution on Dose

38. Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. (**A**)

Dilutions of the Maintenance Concentrate

39. Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. (**D**)

Labeling Dilutions

40. A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. (**D**)

Individualized Treatment Vials

41. Administration of an incorrect injection is a potential risk of allergen immunotherapy. An incorrect injection is an injection given to the wrong patient or a correct patient receiving an injection of an incorrect dose.

    A customized individual maintenance concentrate of the allergen immunotherapy extract and serial dilutions, whether a single extract or a mixture of extracts, prepared and labeled with the patient's name and birth date might reduce the risk of incorrect (i.e., wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for cross contamination of extracts. (**C**)

Starting Doses

42. The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. (**D**)
43. The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. (**D**)

Dose Adjustments for Systemic Reactions

44. The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. (**D**)

Reactions during Periods of Exacerbations and Symptoms

45. Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. (**C**)

Dose Adjustments for Late Injections

46. It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. (**D**)

Cluster Schedules

47. With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. (**C**)

Rush Schedules

48. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. (**A**)

Systemic Reactions and Rush Schedules

49. Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. (**A**)

Premedication and Weekly Immunotherapy

50. Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. (**A**)

Premedication with Cluster and Rush Immunotherapy

51. Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. (**A**)

Maintenance Schedules

52. Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. (**A**)

Continuing Care

<u>Time Course of Improvement</u>

53. Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **(A**)

<u>Follow-Up Visits</u>

54. Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. (**D**)

<u>Duration of Treatment</u>

55. At present, there are no specific tests or clinical markers that will distinguish between patients who will relapse and those who will remain in long-term clinical remission after discontinuing effective inhalant allergen immunotherapy, and the duration of treatment should be determined by the

physician and patient after considering the benefits and risks associated with discontinuing or continuing immunotherapy. (**D**)

Although there are no specific tests to distinguish which patients will relapse after discontinuing VIT, there are clinical features that are associated with a higher chance of relapse, notably a history of very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. (**C**)

The patient's response to immunotherapy should be evaluated on a regular basis. A decision about continuation of effective immunotherapy should generally be made after the initial period of up to 5 years of treatment. (**D**)

The severity of disease, benefits sustained from treatment, and convenience of treatment are all factors that should be considered in determining whether to continue or stop immunotherapy for any individual patient. (**D**)

Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. (**B**)

Documentation and Record Keeping

56. The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. (**D**)

Injection Techniques

57. Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. (**D**)
58. The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. (**D**)

Location of Allergen Immunotherapy Administration

Physician's Office

59. The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. (**D**)
60. Patients at high risk of systemic reactions, where possible, should receive immunotherapy in the office of the physician who prepared the patient's allergen immunotherapy extract. (**D**)

Other Locations

61. Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. (**D**)

Home Administrations

62. In rare and exceptional cases, when allergen immunotherapy cannot be administered in a medical facility and withholding this therapy would result in a serious detriment to the patients' health (e.g., VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient basis. If this approach is used, informed consent should be obtained from the patient, and the person administering the injection to the patient must be educated about how to administer immunotherapy and recognize and treat anaphylaxis. (**D**)
63. If a patient receiving immunotherapy transfers from one physician to another, a decision must be made by the physician to whom the patient has transferred as to whether to continue immunotherapy. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. (**D**)
64. If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. (**D**)
65. A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program from one physician to another. In addition, a record of previous response to and compliance with this program should be communicated to the patient's new physician. (**D**)
66. An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (e.g., aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. (**D**)
67. There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. (**D**)
68. Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. (**D**)

Special Considerations in Immunotherapy

Allergen Immunotherapy in Children

69. Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. (**A**)
70. Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient

must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. (**A**)

Pregnancy

71. Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. (**C**)

Immunotherapy in the Elderly Patients

72. Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. (**D**)

Immunotherapy in Patients with Immunodeficiency and Autoimmune Disorders

73. Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. (**D**)

Alternative Routes of Immunotherapy

Sublingual and Oral Immunotherapy

74. Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. (**A**)
75. Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. (**B**)

Immunotherapy Techniques That Are Not Recommended

76. Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. (**D**)

Definitions:

Category of Evidence*

Ia Evidence from meta-analysis of randomized controlled trials

Ib Evidence from at least 1 randomized controlled trial

IIa Evidence from at least 1 controlled study without randomization

IIb Evidence from at least 1 other type of quasi-experimental study

III Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case control studies

IV Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

LB Evidence from laboratory-based studies

NR Not rated

Strength of Recommendations*

A Directly based on category I evidence

B Directly based on category II evidence or extrapolated from category I evidence

C Directly based on category III evidence or extrapolated from category I or II evidence

D Directly based on category IV evidence or extrapolated from category I, II, or III evidence

NR Not rated

* Adapted with permission from Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. BMJ 1999;318:593-6.

CLINICAL ALGORITHM(S)

An annotated clinical algorithm is provided in the original guideline document for the appropriate use of allergen immunotherapy.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate allergen immunotherapy practices for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity

POTENTIAL HARMS

- The major risk of allergen immunotherapy is anaphylaxis, which in extremely rare cases can be fatal, despite optimal management.
- Patients who are mentally or physically unable to communicate clearly with the physician and patients who have a history of noncompliance might be poor candidates for immunotherapy. If a patient cannot communicate clearly with the physician, it will be difficult for the patient to report signs and symptoms, especially early symptoms, suggestive of systemic reactions.
- Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population.
- Beta-adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of beta-blocker agents and inhalant allergen immunotherapy.

CONTRAINDICATIONS

CONTRAINDICATIONS

Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications for allergen immunotherapy. Examples include severe asthma uncontrolled by pharmacotherapy and significant cardiovascular disease.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients. Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task Force, is authorized to provide an official American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or the ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Chart Documentation/Checklists/Forms
Clinical Algorithm

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. Allergen immunotherapy: a practice parameter second update. J Allergy Clin Immunol 2007 Sep;120(3 Suppl):S25-85. [352 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1996 (revised 2007 Sep)

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Joint Council of Allergy, Asthma and Immunology - Medical Specialty Society

GUIDELINE DEVELOPER COMMENT

These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

SOURCE(S) OF FUNDING

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The rest of the authors have declared that they have no conflict of interest.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Allergen immunotherapy: a practice parameter. American Academy of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 2003 Jan;90(1 Suppl 1):1-40. [210 references]

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Joint Council of Allergy, Asthma, and Immunology (JCAAI) Web site.

Print copies: Available from JCAAI, 50 N. Brockway, Ste 3-3 Palatine, IL 60067.

AVAILABILITY OF COMPANION DOCUMENTS

The appendices of the original guideline document contain a health screening record, allergen immunotherapy administration forms, allergen prescription form, and allergen treatment record.

PATIENT RESOURCES

None available

NGC STATUS

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